Cannabis use during methadone maintenance treatment for opioid use disorder: a systematic review and meta-analysis

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Abstract

Background: Rates of cannabis use among patients receiving methadone maintenance therapy are high, and cannabis use may be associated with outcomes of methadone maintenance therapy. We examined the effect of cannabis use on opioid use in patients receiving methadone maintenance therapy to test the hypothesis that cannabis use is associated with a reduction in opioid use.

Methods: In this systematic review, we searched MEDLINE/PubMed, Embase, PsycINFO, CINAHL and ProQuest Dissertations and Theses Global from inception to July 12, 2018. We summarized the effects of cannabis use on opioid use during methadone maintenance therapy and treatment retention. We conducted meta-analyses using a random effects model.

Results: We included 23 studies in our review. We performed a meta-analysis of 6 studies, with a total number of participants of 3676, examining use of cannabis and opioids during methadone maintenance therapy. Owing to high heterogeneity, we described the studies qualitatively but provide the forest plots as supplemental material. The overall quality of evidence was very low, with a high risk of bias, owing to the nature of observational studies.

Interpretation: We found no consensus among studies that cannabis use is associated with reduced opioid use or longer treatment retention when used during methadone maintenance therapy in patients with opioid use disorder. **PROSPERO Registration:** CRD42015029372

The opioid epidemic related to an increase in prescriptions[1–4] has escalated in the past 2 decades. Opioid use disorder is a fundamental component of this crisis.[5,6] Despite the morbidity and mortality due to opioid use disorder, high rates of HIV infection and hepatitis C among patients with the disorder and high unemployment rates, treatment options are limited in scope and effectiveness.[7,8] Methadone maintenance therapy is the most common treatment for opioid use disorder,[9,10] although other treatments are available.[11] Despite the reported benefits of methadone maintenance therapy in managing opioid use disorder, the number of patients receiving this therapy who continue to use illicit opioids is high.[12] The rates of cannabis use among patients receiving methadone maintenance therapy are higher than those in the general population: about a third of Canadians have used cannabis once in their lifetime,[13] whereas 59.7% of males and 43.5% of females receiving methadone maintenance therapy reported having used cannabis.[14–16] Research suggests that polydrug use (aside from cannabis) is prevalent in the methadone maintenance therapy population.[17,18] There is limited evidence to suggest that cannabis use may reduce opioid use in

pain management[19] but not in opioid use disorder.[20] Studies have shown that, in US states with dispensary-based medical cannabis laws, fewer prescription opioids are dispensed,[21] and there are fewer opioid-related deaths.[22] The US Department of Veterans Affairs has suggested that cannabis should be legalized not only as a mechanism to lower prescription opioid use but also to manage opioid withdrawal.[23] This report made headlines labelling cannabis as an "exit drug."[23]

However, the "exit hypothesis" — the idea that cannabis can be used to manage withdrawal symptoms and therefore help patients with opioid use disorder to stop using opioids – has not been examined systematically. With the legalization of

cannabis in Canada, this question is relevant. We examined the relation between cannabis use and opioid use during methadone maintenance therapy. We focused our question on methadone maintenance therapy as it is the most commonly used treatment for opioid use disorder. We sought to determine 1) whether patients using cannabis during methadone maintenance therapy have lower rates of opioid use during therapy and 2) whether cannabis use improves treatment retention in opioid use disorder.

Methods

This review is presented according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24] It is registered with PROSPERO (no. CRD42015029372). The protocol with detailed methods was published elsewhere.[15] The protocol included our target population, intervention, comparison, outcomes, search terms and a detailed search strategy (Supplemental Table S1, Appendix 1, available at www.cmajopen.ca/content/7/4/E665/suppl/DC1). We provide a summary of the methods below.

Information sources and study selection

We searched MEDLINE/PubMed, Embase, PsycINFO, CINAHL and ProQuest Dissertations and Theses Global from inception to July 12, 2018 for relevant studies. We applied no language or demographic restrictions. We formulated our study question using the PICO (Patient, Intervention, Comparison, Outcome) model: In patients with opioid use disorder receiving methadone maintenance treatment, is cannabis use associated with illicit opioid use, treatment retention, polydrug use, criminal activity or risk behaviours for HIV infection (injection drug use, needle sharing and unprotected sex)? We included both studies with observational designs and those with randomized controlled trial designs.

Data collection

Included studies looked at the association between cannabis use and outcomes of methadone maintenance therapy. To be included, a study had to measure methadone maintenance therapy outcomes by reporting participants' continued opioid use during treatment or treatment retention rates by cannabis use. We excluded studies in which other treatments for opioid use disorder such as buprenorphine were used. We included only methadone maintenance therapy because it was the most commonly used treatment and to avoid the heterogeneity that would have resulted from including different treatment interventions. All articles were screened independently in duplicate at all stages, including data extraction (H.M., C.L., L.Z., M.B. and X.M.Z.). We measured interrater agreement with the κ statistic. Risk of bias was assessed independently in duplicate (H.M., C.L., L.Z., M.B. and X.M.Z.) with the use of the modified Newcastle–Ottawa Scale, as all our included studies were observational by design.[25] We measured the overall quality of the evidence

using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[26]

Statistical analysis

As per our protocol, the intent was to meta-analyze the primary studies and provide quantitative summary estimates. However, when we performed meta-analyses, using random effects taking into account heterogeneity expected in observational studies, the high heterogeneity precluded meaningful conclusions, and therefore we provide a description of the included studies and their findings qualitatively. We determined heterogeneity using the I^2 statistic; a value greater than 40% indicated high heterogeneity.[27]

We used RevMan version 5.3 software (Cochrane Community) for the meta-analyses.[28] Some studies measured cannabis use both before and during treatment, and we chose to use the in-treatment cannabis measurement, as we were interested in how current cannabis use affects outcomes of current methadone maintenance therapy. In studies that included multiple follow-up time points for the outcome measurement, we included the latest follow-up point in the meta-analysis. We did not assess publication bias, as it has been shown that funnel plots do not accurately depict publication bias for meta-analyses that have fewer than 10 studies.[29] However, we provide funnel plots of publication bias for illicit opioid use and treatment retention in Supplemental Figures S1 and S2, respectively, Appendix 1.

We performed a sensitivity analysis by excluding all studies with Newcastle–Ottawa Scale scores of 0 or 1 on individual questions. We performed further subgroup by country and method of cannabis use measurement (subjective v. objective) to further explain any significant heterogeneity found. We were unable to perform subgroup analyses by length of follow-up owing to the limited number of studies.

Ethics approval

As this study was solely literature based, it was not eligible for institutional ethics approval, and none was sought.

Results

Among the 2467 unique citations screened, 23 studies were included in the qualitative synthesis (Figure 1).[13,14,17,20,30–48] Interrater agreement was acceptable for both title/abstract (κ = 0.63, 95% confidence interval 0.57–0.69) and full-text screening (κ = 0.60, 95% confidence interval 0.45–0.74). Although we did not apply any age restrictions, all studies were of adult populations. In studies that reported the proportion of participants with any recent or current (i.e., not lifetime measurements) cannabis use, the prevalence varied from 11.2% to 78.6%.[35,41] As the meta-analyses had high heterogeneity, we present forest plots of illicit opioid use during treatment by cannabis use and treatment retention in Supplemental Figures S3 and S4, respectively, Appendix 1.

Of the 23 studies, 12 looked at continued opioid use,[12–14,30–38] 11 examined treatment retention in relation to using cannabis during methadone maintenance therapy,[13,17,31,32,34,39–43,46]

10 looked at polydrug use,[13,30,31,35,37,43–47] 2 looked at criminal activity,[31,48] and 1 investigated risk behaviours for HIV infection.[43] Additional details, including which variables each study controlled for, are provided in Table 1. We attempted to obtain data necessary to calculate odds ratios when such data were not included in a study. We contacted 12 authors for missing data, but our requests were unmet. Additional details by outcome are presented in Supplemental Table S2, Appendix 1.

All the studies had a moderate or high risk of bias on at least 1 Newcastle–Ottawa Scale criterion. Eight studies did not adjust for any confounding variables.[17,31,33–35,44,46,47] Complete details of the Newcastle–Ottawa Scale ratings are provided in Table 2.
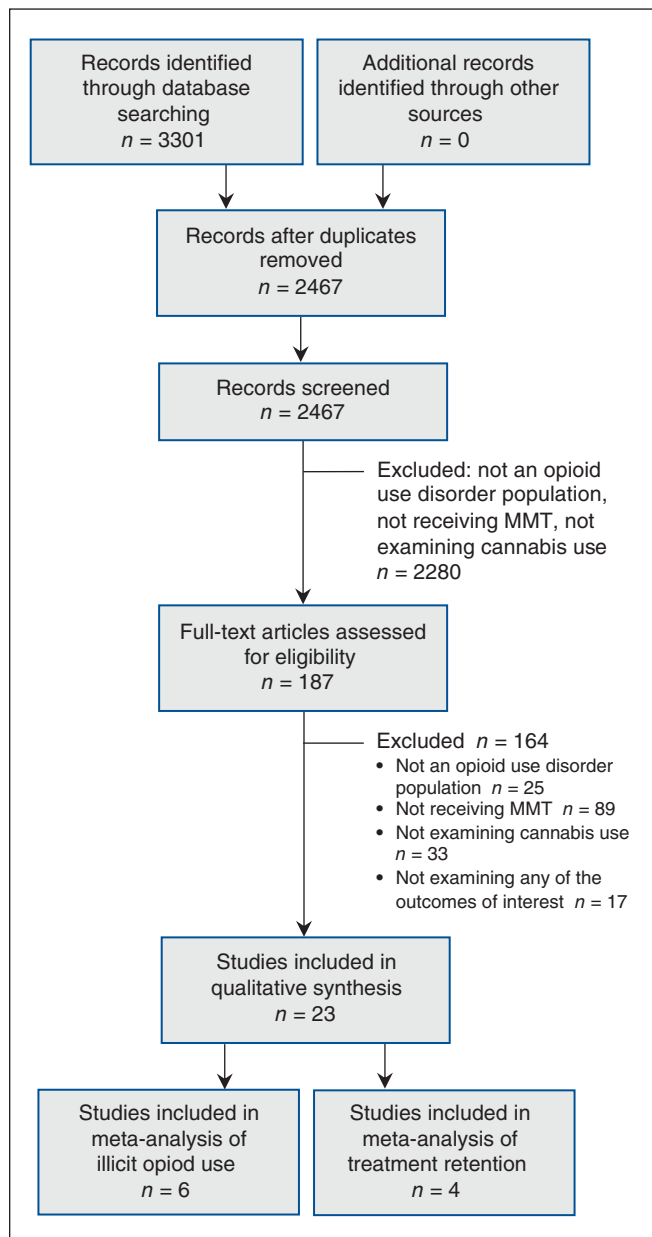

Figure 1: Flow diagram showing selection of included studies. Note: MMT = methadone maintenance treatment.

Continued opioid use

Twelve studies examined the relation between cannabis use and continued opioid use, with a total sample size of 3676.[13,14,20,30–36,38,46] The majority of the studies showed no association between cannabis use and opioid use (Table 1).

There was significant heterogeneity among the studies. These results did not change when we excluded studies with a high risk of bias. Subgroup analyses by country and objective v. subjective measurement of cannabis did not reduce the heterogeneity. We present additional information on these studies in Supplemental Figures S3 and S4, Appendix 1.

The overall quality of evidence was very low, with critical issues of inconsistency and imprecision (Table 3), in addition to a moderate risk of bias. Owing to the nature of observational study designs, GRADE ratings of quality start at low, and any additional concerns in quality assessment make the quality very low.

Treatment retention

Eleven studies investigated cannabis use and retention in methadone maintenance therapy.[13,17,31,32,34,39–43,46] Significant heterogeneity was seen (I^2 = 90%). A sensitivity analysis conducted by excluding studies with high risk of bias to explain heterogeneity did not change the result. In the subgroup analysis by country, we found that studies conducted in the United States showed cannabis use to be significantly associated with decreased retention rates, whereas those conducted in Israel showed the opposite direction. Subgroup analyses by country had an I^2 of 0%, indicating no heterogeneity. The overall quality of evidence was low, with quality issues related to inconsistency and imprecision. The funnel plot is presented in Supplemental Figure S2, Appendix 1.

Secondary outcome measures

Originally, we had aimed to further investigate the association between cannabis use and polydrug use, criminal activity, and risk behaviours for HIV infection and viral hepatitis. For polydrug use, we included 10 studies that investigated the association between cannabis use and use of cocaine, benzodiazepines, alcohol and various forms of cannabis.[13,30,31,35,37,43–48] Owing to the various substances included and outcome measurements, we were unable to combine results for a meta-analysis. Two studies reporting on criminal activity could not be quantitatively analyzed.[31,48] One study reported on cannabis use and HIV infection.[43]

Interpretation

We included 23 studies that examined the association between cannabis use and opioid use and retention in methadone maintenance therapy. Meta-analysis of 6 of these studies showed high heterogeneity that affected the interpretation of the results. The overall quality of evidence was low, with high risk of bias. The results from individual studies suggest that cannabis use may potentially have no effect on opioid use in patients receiving methadone maintenance therapy. The results for treatment retention are inconclusive. We observed a difference

Table 1 (part 1 of 3): Study characteristics							
Investigator, year	Country	Study design	Sample size (% female)	Definition of cannabis use*	Outcome(s) of interest	Statistical analysis	Findings
Best et al.,[30] 1999	UK	Cross-sectional	200 (30)	Categorical: daily users, occasional users (not every day in previous month), nonusers	Illicit opioid use, polydrug use	ANOVA, post hoc Scheffe test, linear regression Factors adjusted for: use of various substances, appetite, overall health, depression, anxiety	Cannabis nonusers had more occasions of heroin use than occasional and daily users Cannabis nonusers consumed significantly more alcohol and crack cocaine than occasional and daily users
Epstein et al.,[31] 2003	US	Secondary analysis (3 separate analyses), 12 mo	408 (40.4)	Dichotomized cannabis use and cannabis abuse/dependence diagnosis	Illicit opioid use, treatment retention, polydrug use, criminal activity	Cox proportional hazards regression Factors adjusted for: not stated Confounders in the regression	No significant association between cannabis use and illicit opioid use No significant association between cannabis use and treatment retention Suggests an association between cocaine abstinence and cannabis use Cannabis use category not associated with any differences in criminal activity
Levine et al.,[32] 2015	US	Retrospective cohort, 1 yr	290 (40.3)	Dichotomized cannabis use	Illicit opioid use, treatment retention	Logistic regression Factors adjusted for: total years of use of various substances	Not significant, but statistics not reported Cannabis-negative urine associated with treatment retention in both men and women
Lions et al.,[33] 2014	France	Secondary RCT analysis, 45 wk	158 (15.2)	Dichotomized: daily users v. nondaily users	Illicit opioid use	Univariate logistic regression Factors adjusted for: not stated	Pretreatment daily cannabis: OR 1.46 (95% CI 0.61–3.77), NS In-treatment daily cannabis: OR 2.81 (95% CI 1.22–6.48)
Nava et al.,[34] 2007	Italy	Prospective cohort, 12 mo	121 (14)	Dichotomized: long-term users (> 6 mo) and currently smoking at least 7 times per week v. nonusers never exposed to marijuana smoking	Illicit opioid use, treatment retention	Hierarchical linear modelling Factors adjusted for: not stated	Significant association between cannabis use and illicit opioid use No significant association between cannabis use and treatment retention
Nirenberg et al.,[35] 1996	US	Prospective cohort, 6 mo	70 (1.4)	Dichotomized cannabis use and categorical (4 groups)	Illicit opioid use, polydrug use	ANOVA Factors adjusted for: not stated	No significant association between cannabis use and illicit opioid use No significant difference in use of cocaine or benzodiazepine between 4 cannabis groups
Proctor et al.,[36] 2016†	US	Retrospective cohort, 12 mo	2410 (40.4)	Dichotomized cannabis use	Illicit opioid use	Logistic regression Factors adjusted for: age, gender, employment status, ethnicity, marital status, average daily methadone dosage	Intake cannabis values in relation to opioid use at 4 time points: 3 mo: OR 1.17 (95% CI 0.83–1.63); 6 mo: OR 0.59 (95% CI 0.32–1.10); 9 mo: OR 0.63 (95% CI 0.24–1.66); 12 mo: OR 0.23 (95% CI 0.05–1.16)

in the association between cannabis use and retention in methadone maintenance therapy in a subgroup analysis by country, specifically between studies conducted in the US and Israel. A previous study showed differences in retention in opioid use disorder treatment between Israel and the US, arguably due to various sociodemographic factors.[41] However, given the conflicting findings by region, the overall effect of cannabis use on treatment retention in opioid use disorder is unknown.

The differences between our results and those of other investigators likely reflect how cannabis use was measured.

Table 1 (part 2 of 3): Study characteristics							
Investigator, year	Country	Study design	Sample size (% female)	Definition of cannabis use*	Outcome(s) of interest	Statistical analysis	Findings
Saxon et al.,[37] 1996	US	Prospective cohort, 18 mo	353 (38.2)	Categorical: 7-point scale ranging from 0 (never) to 6 (≥ 4 times per day)	Illicit opioid use, treatment retention, polydrug use	Cox regression model Factors adjusted for: age, gender, previous methadone treatment, substance use	No significant association between cannabis use, and illicit opioid use or treatment retention Significant association between cannabis use and cocaine use
Scavone et al.,[13] 2013	US	Retrospective cohort, 9 mo	91 (36.6)	Dichotomized cannabis use	Illicit opioid use, treatment retention, polydrug use	ANCOVA, parallel ANCOVA Factors adjusted for: daily opioid expenditure	No significant relation between frequency of cannabis use in treatment and opiate use No significant association between cannabis use and treatment retention Correlation between rates of cannabis use and illicit benzodiazepine use
Somers et al.,[38] 2012	Ireland	Retrospective cohort, 15 mo	123 (NR)	Dichotomized cannabis use	Illicit opioid use	Logistic regression Factors adjusted for: variables that were significant from univariate analysis, did not explicitly state which ones	Baseline: OR 0.88 (95% CI 0.67–1.15); 3 mo: OR 0.79 (95% CI 0.58–1.10); 9 mo: OR 0.78 (95% CI 0.55–1.20); 15 mo: OR 1.45 (95% CI 0.82–2.50); Total: adjusted OR 0.32 (95% CI 0.06–1.66)
Wasserman et al.,[20] 1998	US	Prospective cohort, 6 mo	74 (40.5)	Dichotomized cannabis use	Illicit opioid use	Cox proportional hazards regression Factors adjusted for: abstinence goals, positive moods, pleasant events, negative moods, life events, perceived stress, opioid withdrawal symptoms	Significant association between cannabis use and illicit opioid use
Zielinski et al.,[14] 2017	Canada	Cross-sectional	777 (46.7)	Dichotomized cannabis use in previous 30 d	Illicit opioid use	Multivariable logistic regression analysis Factors adjusted for: age, gender, methadone dosage, treatment duration	No significant association between cannabis use and illicit opioid use
Joe et al.,[39] 1998	US	Prospective cohort, 360 d	981 (39)	Dichotomized: at least weekly marijuana use or not	Treatment retention	Hierarchical linear regression model Factors adjusted for: age, ethnicity, marital status, legal status, employment status, number of lifetime arrests	No significant association between cannabis use and treatment retention
Peles et al.,[40] 2006	Israel	Prospective cohort, 11 yr	492 (27.2)	Dichotomized cannabis use	Treatment retention	Fisher exact test, Cox regression analysis Factors adjusted for: age, children, methadone dosage, use of various substances	No significant association between cannabis use and treatment retention
Peles et al.,[41] 2008	US, Israel	Prospective cohort, 12 mo	794 (31.0)	Dichotomized cannabis use	Treatment retention	Kaplan–Meier survival analysis with log rank for cumulative retention, Cox regression Factors adjusted for: methadone dosage, age	No significant association between cannabis use and treatment retention

Table 1 (part 3 of 3): Study characteristics							
Investigator, year	Country	Study design	Sample size (% female)	Definition of cannabis use*	Outcome(s) of interest	Statistical analysis	Findings
Schiff et al.,[42] 2007	Israel	Retrospective cohort, 13 mo	2683 (14.1)	Dichotomized cannabis use	Treatment retention	Logistic regression Factors adjusted for: age, gender	Significant relation between cannabis use and increased treatment retention
Weizman et al.,[43] 2004	Israel	Prospective cohort, 12 mo	283 (NR)	Dichotomized: cannabis abuse v. not	Treatment retention, polydrug use, risk behaviours for HIV infection	Cox regression survival analysis Factors adjusted for: heroin, cocaine and benzodiazepine abuse	No significant association between cannabis use and treatment retention Significant association between cannabis use and use of benzodiazepine, amphetamine and cocaine Cannabis use was not related to any risk behaviours (statistics not reported)
White et al., 2014[17]	US	Retrospective cohort, 15–17 mo	604 (39.4)	Dichotomized cannabis use	Treatment retention	χ^2 test, Fisher exact test Factors adjusted for: not stated	At baseline, cannabis use was significantly associated with treatment retention
Bleich et al.,[44] 1999	Israel	Prospective cohort, 12 mo	148 (29.8)	Positive result of urine test for cannabis during 12th mo of treatment‡	Polydrug use	χ^2 test Factors adjusted for: not stated	Benzodiazepine abusers were more likely to currently abuse cannabis than nonabusers of benzodiazepine
Peirce et al.,[45] 2009	US	Secondary RCT analysis, 12 wk	386 (44)	Cannabis use, defined as positive result of testing of urine/ breath sample obtained at study intake	Polydrug use	Mixed-model regression Factors adjusted for: age, gender, ethnicity, employment status, criminal activity, additional demographic factors	Significant association between cannabis use and stimulant use
Saxon et al.,[46] 1993	US	Cross-sectional	98 (0)	Dichotomized cannabis use	Polydrug use	Mann–Whitney test Factors adjusted for: not stated	Significant association between cannabis use and other drug use
Strain et al.,[47] 1991	US	Cross-sectional	66 (45)	Dichotomized: those with v. without history of cannabis use diagnosis	Polydrug use	Z-test Factors adjusted for: not stated	No significant association between cannabis use and use of alcohol, sedatives and cocaine
Bell et al.,[48] 1997	Australia	Prospective cohort, 12 mo	304 (43.1)	Continuous: average daily use of cannabis in previous month	Criminal activity	Multiple linear regression Factors adjusted for: age, gender, employment, benzodiazepine use, cost of drugs	Cannabis use was significant predictor of criminal activity at 12 mo

Note: ANCOVA = analysis of covariance, ANOVA = analysis of variance, CI = confidence interval, NR = not reported, NS = not significant, OR = odds ratio, RCT = randomized controlled trial.
*"Dichotomized cannabis use" means users versus nonusers or at least 1 positive urine screen result versus none, unless specified otherwise.
†This study had too many results to present in this table, so we included only intake cannabis values in relation to opioid use at all time points. See study for more results.
‡An abuser of any substance of abuse was defined as having a positive urine test result for that substance during the 12th month of treatment.

For instance, studies in our review dichotomized cannabis use in some way, categorizing people based on any cannabis use versus no use or grouping those who used more than a certain amount of cannabis versus those who used less. This choice of measurement was likely made because estimating the amount and type/strength/concentration of cannabis is challenging,[49] and it makes the establishment of a dose–response relation in any of these studies impossible.[50] This choice could obscure an association in either direction. Heavy use of cannabis has been reported to be associated with adverse health effects.[51,52] The studies in our systematic review did not distinguish between cannabis use disorder and recreational cannabis use. Compared to recreational users, patients with cannabis use disorder have high rates of comorbid psychiatric disorders,[53] which are associated with poorer treatment outcomes.[54] Peirce and colleagues[45] suggested that a

Table 2: Risk of bias assessment using the modified Newcastle–Ottawa Scale

Investigator	Selection bias: is source population representative?	Performance bias		Detection bias		Information bias		Total score*
		Is sample size sufficient, is there sufficient power?	Did study adjust for confounders?	Did study use appropriate statistical analysis?	Are there few missing data, was this handled appropriately?	Outcome measurement appropriate?	Objective assessment of outcome of interest?	
Bell et al.[48]	2	2	3	3	2	2	2	16
Best et al.[30]	2	3	2	1	1	2	0	11
Bleich et al.[44]	1	1	0	1	1	1	3	8
Epstein et al.[31]	0	1	0	3	2	3	3	12
Joe et al.[39]	3	3	3	3	2	3	3	20
Levine et al.[32]	2	2	2	2	1	3	3	15
Lions et al.[33]	1	2	0	2	1	3	2	11
Nava et al.[34]	0	1	0	2	1	2	3	9
Nirenberg et al.[35]	2	1	0	1	1	3	3	11
Peirce et al.[45]	1	3	3	3	3	3	3	19
Peles et al.[40]	3	3	3	3	3	3	3	21
Peles et al.[41]	3	3	3	3	3	3	3	21
Proctor et al.[36]	3	3	3	1	1	3	3	17
Saxon et al.[46]	1	1	0	1	1	2	3	9
Saxon et al.[37]	2	2	3	2	2	2	3	16
Scavone et al.[13]	1	1	3	1	2	1	2	11
Schiff et al.[42]	3	3	2	3	2	3	3	19
Somers et al.[38]	2	1	1	1	2	1	3	11
Strain et al.[47]	2	0	0	1	2	2	1	8
Wasserman et al.[43]	2	0	3	3	3	3	3	17
Weizman et al.[43]	2	2	2	1	1	1	3	12
White et al.[17]	2	3	0	1	2	2	3	13
Zielinski et al.[14]	3	3	3	3	1	2	3	18

*0 = definitely no (high risk of bias), 1 = mostly no (met a little of the criterion), 2 = mostly yes (met most of the criterion), 3 = definitely yes (low risk of bias). Maximum total score 21.

diagnosis of cannabis use disorder in the previous 12 months is associated with less stimulant drug use during methadone maintenance therapy, whereas recent (in the previous month) cannabis use is associated with more stimulant use. Their study shows that the recency of cannabis use may affect the use of other drugs during methadone maintenance therapy. It is possible that patients in that study who used cannabis had more severe opioid-related problems or other factors driving their use, such as pain, which would have created a confounding effect; hence, the differences seen in the association of cannabis use with opioid use may have varied by the population of interest (e.g., pain or addiction cohorts).

Our findings suggest that cannabis use does not affect treatment outcomes for patients receiving methadone maintenance therapy. In these cases, it was not an exit drug. The broad negative health effects of heavy cannabis use have been well documented.[51,52] We should continue to counsel patients on the potential risks of cannabis use while emphasizing that we have no evidence to support the use of cannabis in opioid use disorder treatment. Previous studies showed that, in jurisdictions with medical cannabis laws, fewer prescription opioids were issued.[21,22] Even in populations with pain conditions and not opioid addiction, those observations do not show that a reduction in opioid prescription was solely due to cannabis as a replacement for opioids.[21,22] A national cohort study investigating cannabis use in patients prescribed opioids for pain showed that cannabis use did not reduce opioid use and was associated with worse pain control and psychiatric symptoms.[55]

Table 3: Grading of Recommendations Assessment, Development and Evaluation evidence profile for primary outcomes

Outcome, no. of studies	Quality assessment						Quality	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Illicit opioid use, 7	Observational studies	Serious*	Very serious†‡	Not serious	Very serious§	None	⊕OOO VERY LOW	CRITICAL
Retention, 4	Observational studies	Not serious	Serious†	Not serious	Very serious§	None	⊕OOO VERY LOW	CRITICAL

*Moderate risk of bias across studies.
†Point estimates vary widely across studies, little overlap between individual confidence intervals.
‡Heterogeneity not explained by subgroup analyses.
§Small samples, wide pooled 95% confidence interval.

Further studies are needed to address the notion of cannabis use as a substitute for opioid use, whether for pain or for opioid use disorder. We need more research to understand the relations between opioid use, treatment outcomes and cannabis use in opioid use disorder. More investigation is needed to reconcile the findings of the prescription pattern studies with those of the patient population studies. The observational nature of the studies means that confounders such as the association of cannabis use with severity of opioid addiction or pain could obscure significant relations. Further research should include detailed definitions of cannabis use.

Limitations

There are limitations to be taken into consideration when interpreting our findings. The results come from small to medium-sized observational studies with limited data on confounding variables. For example, cannabis is seldom used alone; it is associated with polydrug use and with comorbid substance use disorders in patients receiving methadone maintenance therapy.[43,56,57] Polydrug use and substance use disorders are associated with poorer outcomes in opioid use disorder.[58] There were also methodological limitations. Our meta-analyses had substantial heterogeneity, partly because of methodological variability: there were differences in methadone maintenance therapy duration, associated psychosocial interventions, definition of cannabis use and outcome measures. Our subgroup analyses did not explain this heterogeneity for continued opioid use. The limited number of studies included in the meta-analyses precluded further subgroup analyses to identify other possible sources of heterogeneity, such as length of follow-up. Given the nature of observational studies, there are likely to be other sources of heterogeneity that cannot be detected because unknown confounding variables affect the outcomes. Finally, we were unable to do a complete grey literature search.

Conclusion

We found no consensus among studies that cannabis use is associated with reduced opioid use or longer treatment retention when used during methadone maintenance therapy in patients with opioid use disorder. The study limitations must be taken into account when interpreting these results. Further studies are needed to address and examine the notion of cannabis use and its effect on treatment outcomes in patients with opioid use disorder.

References

1. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA* 2008;300:2613-20.
2. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose a cohort study. *Ann Intern Med* 2010;152:85-92.
3. Paulozzi LJ, Ryan GW. Opioid analgesics and rates of fatal drug poisoning in the United States. *Am J Prev Med* 2006;31:506-11.
4. Emergency department visits involving nonmedical use of selected prescription drugs, United States, 2004–2008. *MMWR Morb Mortal Wkly Rep* 2010;59:705-9.
5. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health* 2015;36:559-74.
6. Han B, Compton WM, Jones CM, et al. Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003–2013. *JAMA* 2015;314:1468-78.
7. Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. *Harv Rev Psychiatry* 2015;23:63-75.
8. Socías ME, Ahamad K. An urgent call to increase access to evidence-based opioid agonist therapy for prescription opioid use disorders. *CMAJ* 2016;188:1208-9.
9. Farré M, Mas A, Torrens M, et al. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug Alcohol Depend* 2002;65:283-90.
10. MacArthur GJ, Minozzi S, Martin N, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. *BMJ* 2012;345:e5945.
11. Bruneau J, Ahamad K, Goyer MÈ, et al. Management of opioid use disorders: a national clinical practice guideline. *CMAJ* 2018;190:E247-57.
12. Shahid H, Bhatt M, Sanger N, et al. Association between family factors and illicit polysubstance use amongst methadone maintenance patients with opioid use disorder. *Int J High Risk Behav Addict* 2018;7:e58786.
13. Scavone JL, Sterling RC, Weinstein SP, et al. Impact of cannabis use during stabilization on methadone maintenance treatment. *Am J Addict* 2013;22:344-51.
14. Zielinski L, Bhatt M, Sanger N, et al. Association between cannabis use and methadone maintenance treatment outcomes: an investigation into sex differences. *Biol Sex Differ* 2017;8:8.
15. Zielinski L, Bhatt M, Eisen RB, et al. Association between cannabis use and treatment outcomes in patients receiving methadone maintenance treatment: a systematic review protocol. *Syst Rev* 2016;5:139.
16. Timko C, Schultz NR, Cucciare MA, et al. Retention in medication-assisted treatment for opiate dependence: a systematic review. *J Addict Dis* 2016;35:22-35.
17. White WL, Campbell MD, Spencer RD, et al. Patterns of abstinence or continued drug use among methadone maintenance patients and their relation to treatment retention. *J Psychoactive Drugs* 2014;46:114-22.
18. Taylor OD. Poly substance use in methadone maintenance therapy (MMT) patients. *J Hum Behav Soc Environ* 2015;25:822-9.
19. Vowles KE, McEntea ML, Julnes TF, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain* 2015;156:569-76.
20. Wasserman DA, Weinstein MG, Havassy BE, et al. Factors associated with lapses to heroin use during methadone maintenance. *Drug Alcohol Depend* 1998;52:183-92.

21. Bradford AC, Bradford WD, Abraham A, et al. Association between US state medical cannabis laws and opioid prescribing in the Medicare part D population. *JAMA Intern Med* 2018;178:667-72.
22. Bachhuber MA, Saloner B, Cunningham CO, et al. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999–2010. *JAMA Intern Med* 2014;174:1668-73.
23. Angell T. V.A. issues new medical marijuana policy for military veterans. *Forbes* 2017 Dec. 19. Available: https://www.forbes.com/sites/tomangell/2017/12/19/v-a-issues-new-medical-marijuana-policy-for-military-veterans/#6d1ff4215b90 (accessed 2019 Oct. 29).
24. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6: e1000097.
25. Bawor M, Dennis BB, Anglin R, et al. Sex differences in outcomes of methadone maintenance treatment for opioid addiction: a systematic review protocol. *Syst Rev* 2014;3:45.
26. Guyatt GH, Oxman AD, Schünemann HJ, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011; 64:380-2.
27. Higgins J, Green S, editors. *Cochrane handbook for systematic reviews of interventions. Version 5.1.0* [updated March 2011]. Oxford (UK): Cochrane Collaboration; 2011.
28. Stang A. Critical evaluation of the Newcastle–Ottawa Scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603-5.
29. Lau J, Ioannidis JPA, Terrin N, et al. Evidence based medicine: the case of the misleading funnel plot. *BMJ* 2006;333:597.
30. Best D, Gossop M, Greenwood J, et al. Cannabis use in relation to illicit drug use and health problems among opiate misusers in treatment. *Drug Alcohol Rev* 1999;18:31-8.
31. Epstein DH, Preston KL. Does cannabis use predict poor outcome for heroin-dependent patients on maintenance treatment? Past findings and more evidence against. *Addiction* 2003;98:269-79.
32. Levine AR, Lundahl LH, Ledgerwood DM, et al. Gender-specific predictors of retention and opioid abstinence during methadone maintenance treatment. *J Subst Abuse Treat* 2015;54:37-43.
33. Lions C, Carrieri MP, Michel L, et al. Predictors of non-prescribed opioid use after one year of methadone treatment: an attributable-risk approach (ANRS–Methaville trial). *Drug Alcohol Depend* 2014;135:1-8.
34. Nava F, Manzato E, Lucchini A. Chronic cannabis use does not affect the normalization of hypothalamic–pituitary–adrenal (HPA) axis induced by methadone in heroin addicts. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; 31:1089-94.
35. Nirenberg TD, Cellucci T, Liepman MR, et al. Cannabis versus other illicit drug use among methadone maintenance patients. *Psychol Addict Behav* 1996; 10:222-7.
36. Proctor SL, Copeland AL, Kopak AM, et al. Outcome predictors for patients receiving methadone maintenance treatment: findings from a retrospective multi-site study. *J Subst Use* 2016;21:601-13.
37. Saxon AJ, Wells EA, Fleming C, et al. Pre-treatment characteristics, program philosophy and level of ancillary services as predictors of methadone maintenance treatment outcome. *Addiction* 1996;91:1197-209.
38. Somers CJ, O'Connor J. Retrospective study of outcomes, for patients admitted to a drug treatment centre board. *Ir Med J* 2012;105:295-8.
39. Joe GW, Simpson DD, Broome KM. Effects of readiness for drug abuse treatment on client retention and assessment of process. *Addiction* 1998;93:1177-90.
40. Peles E, Schreiber S, Adelson M. Factors predicting retention in treatment: 10-year experience of a methadone maintenance treatment (MMT) clinic in Israel. *Drug Alcohol Depend* 2006;82:211-7.
41. Peles E, Linzy S, Kreek MJ, et al. One-year and cumulative retention as predictors of success in methadone maintenance treatment: a comparison of two clinics in the United States and Israel. *J Addict Dis* 2008;27:11-25.
42. Schiff M, Levit S, Moreno RC. Retention and illicit drug use among methadone patients in Israel: a gender comparison. *Addict Behav* 2007;32:2108-19.
43. Weizman T, Gelkopf M, Melamed Y, et al. Cannabis abuse is not a risk factor for treatment outcome in methadone maintenance treatment: a 1-year prospective study in an Israeli clinic. *Aust N Z J Psychiatry* 2004;38:42-6.
44. Bleich AVI, Gelkopf M, Schmidt V, et al. Correlates of benzodiazepine abuse in methadone maintenance treatment: a 1-year prospective study in an Israeli clinic. *Addiction* 1999;94:1533-40.
45. Peirce JM, Petry NM, Roll JM, et al. Correlates of stimulant treatment outcome across treatment modalities. *Am J Drug Alcohol Abuse* 2009;35:48-53.
46. Saxon AJ, Calsyn DA, Greenberg D, et al. Urine screening for marijuana among methadone-maintained patients. *Am J Addict* 1993;2:207-11.
47. Strain EC, Brooner RK, Bigelow GE. Clustering of multiple substance use and psychiatric diagnoses in opiate addicts. *Drug Alcohol Depend* 1991;27:127-34.
48. Bell J, Mattick R, Hay A, et al. Methadone maintenance and drug-related crime. *J Subst Abuse* 1997;9:15-25.
49. van der Pol P, Liebregts N, de Graaf R, et al. Validation of self-reported cannabis dose and potency: an ecological study. *Addiction* 2013;108:1801-8.
50. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. *Neuroscience* 2013; 248:637-54.
51. Volkow ND, Baler RD, Compton WM, et al. Adverse health effects of marijuana use. *N Engl J Med* 2014;370:2219-27.
52. Volkow ND, Swanson JM, Evins AE, et al. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. *JAMA Psychiatry* 2016;73:292-7.
53. Khan SS, Secades-Villa R, Okuda M, et al. Gender differences in cannabis use disorders: results from the national epidemiologic survey of alcohol and related conditions. *Drug Alcohol Depend* 2013;130:101-8.
54. Rosic T, Naji L, Bawor M, et al. The impact of comorbid psychiatric disorders on methadone maintenance treatment in opioid use disorder: a prospective cohort study. *Neuropsychiatr Dis Treat* 2017;13:1399-408.
55. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. *Lancet Public Health* 2018;3:e341-50.
56. Degenhardt L, Hall W, Lynskey M. The relationship between cannabis use and other substance use in the general population. *Drug Alcohol Depend* 2001; 64:319-27.
57. Blanco C, Hasin DS, Wall MM, et al. Cannabis use and risk of psychiatric disorders: prospective evidence from a US national longitudinal study. *JAMA Psychiatry* 2016;73:388-95.
58. Kelly SM, O'Grady KE, Mitchell SG, et al. Predictors of methadone treatment retention from a multi-site study: a survival analysis. *Drug Alcohol Depend* 2011; 117:170-5.

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